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(54) Title: DRUG FORMULATIONS HAVING REDUCED ABUSE POTENTIAL

(57) Abstract: Drug formulations having reduced abuse potential which contain one or more of (1) an agent that has a nasty odor, (2) a bright deterrent/indicator dye and (3) fine insoluble particulate matter. The malodorous agent and dye are in a form which does not affect proper administration of the drug, but the odorous agent creates a nasty odor when the dosage form is crushed or chemically extracted and nasally, by inhalation, orally, buccally or sublingually administered and the dye produces a bright color when crushed and contacted. The fine insoluble particulate matter hinders extraction of the drug from the dosage form and, when crushed, can deter intravenous injection because of the presence of the insoluble particles or hinder injection by blocking an intravenous needle. The bright color of the dye, when extracted, also has a psychologically deterrent effect on intravenous abusers.

WO 2004/100894 A2

DRUG FORMULATIONS HAVING REDUCED ABUSE POTENTIAL

FIELD OF THE INVENTION

[0001]

This invention relates to dosage forms of prescription psychoactive drug formulations having a reduced potential for abuse and to methods of reducing the potential for abuse of dosage forms of prescription psychoactive drugs.

BACKGROUND OF THE INVENTION

[0002]

Prescription psychoactive drugs can help patients manage chronic or severe pain, restore emotional or behavioral balance, control sleep disorders, or fight obesity. When such prescription medications are abused, however, the consequences, including addiction, can be dangerous, even deadly. The risks associated with abuse of three classes of commonly abused prescription drugs, i.e., opioids; central nervous system (CNS) depressants, including sedatives and tranquilizers; and stimulants, are well documented.

[0003]

Opioids include morphine, codeine, and related drugs such as oxycodone (Percodan and OxyContin), hydrocodone (Vicodin), and meperidine (Demerol) and are commonly prescribed to relieve pain. Taken as prescribed, opioids can be used to manage pain effectively without untoward side effects. Chronic use of opioids can result in tolerance, which means that users must take higher doses to achieve the same effects. Long-term use also can lead to physical dependence and addiction. Withdrawal can occur when an individual discontinues use of the drugs. Withdrawal symptoms can include restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps, and involuntary leg movements. Individuals who are addicted to opioids are more likely to overdose on the drugs,

which could be fatal.

[0004]

Among the most commonly prescribed CNS depressants are barbiturates, such as mephobarbital (Mebaral) and pentobarbital sodium (Nembutal), which are prescribed to treat anxiety, tension, and sleep disorders; and benzodiazepines, such as diazepam (Valium) and alprazolam (Xanax), which typically are prescribed to treat anxiety, acute stress reactions, and panic attacks. Other benzodiazepines, such as triazolam (Halcion) and estazolam (ProSom), are prescribed for short-term treatment of sleep disorders. Although the various classes of CNS depressants work differently, they all produce a beneficial drowsy or calming effect in individuals suffering from sleep disorders or anxiety. However, if one uses these drugs over a long period of time, the body will develop tolerance, and larger doses will be needed to achieve the initial effects. In addition, continued use can lead to physical dependence and, when use is reduced or stopped, withdrawal. Both barbiturates and benzodiazepines have the potential for abuse and should be used only as prescribed. As with opioids, an overdose of these drugs can be fatal.

[0005]

Stimulants increase heart rate, blood pressure and metabolism, provide feelings of exhilaration and energy, and increase mental alertness. Stimulants such as methylphenidate (Ritalin) and dextroamphetamine (Adderall and Dexedrine) are prescribed for the treatment of narcolepsy, attention-deficit/hyperactivity disorder, and depression that has not responded to other treatments. They also may be used for short-term treatment of obesity. Individuals may become addicted to the sense of well-being and enhanced energy that stimulants can generate. Taking high doses of stimulants repeatedly over a short time, however, can lead to feelings of hostility or

paranoia. Additionally, taking high doses of stimulants may result in dangerously high body temperatures and an irregular heartbeat.

[0006]

Abuse potential of these three classes of drugs is of major concern. This is specially true for opioids and stimulants and hence they are classified by the Drug Enforcement Agency (DEA) as Schedule II drugs (substances that have a high potential for abuse with severe liability to cause psychic or physical dependence, but have some approved medical use).

[0007]

Various dosage forms of psychoactive drugs for medical use are available or possible. These include capsules, tablets, transdermal patches and liquid suspensions. For example, methylphenidate (Ritalin) is available in oral, tablet and extended-release tablet dosage forms. Dextroamphetamine (Adderall) is available in immediate-release tablet and extended-release capsule dosage forms. Methylphenidate, amphetamine, fentanyl, 3-methyl fentanyl, morphine, etorphine, etc. can be incorporated into transdermal patches. A fentanyl patch (Duragesic) is already in the marketplace and a methylphenidate patch (Methypatch) is under FDA review. Liquid suspensions of drugs in immediate release and sustained release forms are also possible. A sustained release system can be formulated by using drug ion-exchange complex particles with a further coating of ethyl cellulose. The ion-exchange technology makes reliable liquid controlled-release possible for many ionic drugs, which include amphetamine, methylphenidate, hydrocodone, codeine, morphine, and the like.

[0008]

These various dosage forms provide valuable medical benefits when properly taken or administered, but also have a

high potential for abuse. For example, sustained release dosage forms are abused by crushing or chewing and then swallowing or snorting or by mixing or dissolving in water or the like and then injecting. Transdermal patches can be chewed to provide a quick onset via buccal, sublingual, or oral absorption of the controlled substances. In addition, a significant drug residue after normal administration of the patches is quite common. Such residue can be extracted and concentrated for abuse. Liquid suspensions can be similarly concentrated and abused.

[0009]

It view of these problems, new and improved dosage forms of psychoactive drugs having decreased abuse potential are desired. Several approaches to reducing the abuse potential of dosage forms of drugs can be found in U.S. patents. These include, for example, the incorporation of an opioid antagonist into a dosage form (U.S. Patent Nos. 4401672, 4457933, 5162341, 5236714, 6277384 and 6228863), the use of cytochrome P450 2D6 enzyme inhibitor (U.S. Patent No. 6124282), and the incorporation of a water soluble/gelable material into a dosage form (U.S. Patent No. 4070494). However, these approaches still are far from ideal in terms of the effectiveness of deterring someone from abusing the medication by snorting or smoking or improper oral administration.

OBJECT OF THE INVENTION

[0010]

It is an object of the present invention to reduce the potential for abuse of dosage forms of psychoactive drugs and other drugs of abuse and to provide dosage forms of psychoactive drugs having a reduced potential for abuse. More particularly, it is an object of the present invention to provide oral dosage forms of opioids, CNS depressants and stimulants that have increased effectiveness in deterring abuse by snorting/injecting or the like.

SUMMARY OF THE INVENTION

[0011]

According to the present invention dosage forms of psychoactive drugs, which have reduced abuse potential are provided by adding one or more of the following to the dosage forms:

(1) an agent in a form which does not create a nasty odor when a dosage form of the drug is properly administered, but which creates a nasty odor when the dosage form is crushed or chemically extracted for nasal (snorting), inhalation (smoking), oral, buccal or sublingual administration;

(2) a bright deterrent/indicator dye in a form which does not create color when a dosage form of the drug is properly administered, but which colors or stains the nose, mouth or hands when the dosage form is crushed or chemically extracted; and

(3) fine insoluble particulate matter which does not adversely affect the human body when a dosage form of the drug is properly administered, but which hinders extraction of the drug from the dosage form and can deter intravenous injection because of the presence of the insoluble particles or hinder injection by blocking the intravenous needle.

DETAILED EXPLANATION OF THE INVENTION

[0012]

The psychoactive drug (i.e., a drug that affects the central nervous system) of the dosage form of the present invention is not particularly limited insofar as the drug is approved for medical use in dosage form and has a potential for abuse. The drug includes opioids, central nerve system (CNS) depressants and stimulants such as, for example, drugs sold commercially under the trademarks Adderall XR, Matadate CD, Kadian, Oramorph SR, MS Contin, Oxycontin and the like.

[0013]

Snorting and smoking for substance abuse are widespread and the use of chemicals with a nasty odor in preparation of abuse-potential drug product can be an effective means to deter the drug abuse. The malodorous agent and/or indicator dye to be incorporated into the dosage forms of the present invention is used in a form which does not exhibit its deterrent effect when a dosage form of the drug is properly administered, but exhibits a deterrent effect when the dosage form is chewed, crushed or chemically extracted for nasal (snorting), inhalation (smoking), oral, buccal or sublingual administration. The malodorous agent and/or indicator dye can be incorporated into granules, beads, or mini-tablets which can be subsequently coated with a suitable barrier coating to prevent against leakage of the malodorous agent and indicator dye and to minimize or prevent absorption of the malodorous agent and indicator dye under normal dosage administration conditions. These granules/beads/mini-tablets can be encapsulated or compressed with the drug of interest or can be used as coating substrates for drug layering and further enteric/sustained-release coatings.

[0014]

The sizes of the granules, beads and mini-tablets is not limited as long as the granules can be incorporated into the dosage forms of the invention. Typically, the granules and beads have a size of 50μm to 4000μm. The mini-tablets have a size which is typically significantly smaller than common tablets (>5/32 inch diameter). When granules, beads or mini-tablets containing an agent with a nasty odor and/or a dye indicator and not containing a drug are encapsulated with granules, beads or mini-tablets containing an active pharmaceutical ingredient (API), the granules, beads or mini-tablets are preferably of the same size to make it difficult for the respective beads to be distinguished and separated.

[0015]

Alternatively, the malodorous agent and/or indicator dye can be incorporated directly into a drug formulation and the resultant formulation incorporated into granules, beads, or mini-tablets. Subsequently, a barrier coating is applied to ensure against leakage of the malodorous agent and indicator dye under normal dosage administration conditions. The resultant coated granules, beads or mini-tablets of the drug formulation are thereafter encapsulated or compressed into tablets.

[0016]

When used in a transdermal patch formulation, the malodorous agent and/or indicator dye can be used in the form of the above-described granules, beads, or mini-tablets coated with a suitable barrier coating. The malodorous agent can also be added directly to the transdermal drug formulation.

[0017]

The malodorous agent useful in the present invention includes any pharmaceutically acceptable substance or substances that create a nasty odor or side effect when administered nasally (snorted), by inhalation (smoking), orally, bucally or sublingually. Such agents include, but are not limited to, valerian herb crude extract, isovaleric acid, betaine, anisole, garlic oil, garlic crude extract, fish oil, skatole, methylarginine, taurine, trimethylamine, triethylamine, 3-methyl 2-hexanoic acid, and the like. The preferred agents are isovaleric acid and skatole. Isovaleric acid occurs in hop oil, tobacco, valerian herb, and several other plants. Isovaleric acid has a disagreeable, rancid-cheese odor. Skatole is white to brownish scales with a strong fecal odor. When a product contains skatole or isovaleric acid, it has such an intensely nasty odor it is extremely difficult for a person to inhale or snort it.

[0018]

The agent having a nasty odor is used in an amount of from 0.10 to 20% by weight and, preferably, 1.0 to 10% by weight and, most preferably, 1.0 to 5.0% by weight based on the weight of a dosage form of the pharmaceutical formulation into which the agent is incorporated. The agent can be one or more of the above-noted substances. The malodorous aversion agent in non-releasable form is preferred, because the aversion agent is not released from an intact unit (e.g., heavily coated mini-tablets or pellets containing the aversion agent), has no pharmacological effect, and has no impact on the release profile of the active ingredient. The aversion agent can be incorporated into a dosage form with the active ingredient as a releasable form of the aversion agent, which can have similar release patterns, such as delayed-release and sustained release, to the drug.

[0019]

The indicator dye useful in the invention includes any dye that is pharmaceutically acceptable and that is capable of providing an intense, bright color on the nose, mouth and hands after a pharmaceutical formulation containing the dye is crushed or dissolved. The bright color also can have a psychologically deterrent effect on intravenous abusers. Such dyes include, but are not limited to allura red, amaranth, brilliant blue, canthaxanthin, carmine, carmoisine, carotene, curcumin, erythrosine, green S, indigo carmine, iron oxide black, iron oxide red, iron oxide yellow, patent blue, phloxine O, ponceau 4R, quinoline yellow, riboflavin, sunset yellow, tartrazine, titanium dioxide, vegetable carbon black, and other natural colors such as annatto, beet, black carrot, black currant, caramel, carmine, carmine lake, chlorophyll, cochineal, elderberry, grapeskin/grape juice, malt, paprika, red cabbage, turmeric, and anthocyanins. Riboflavin is a preferred indicator because it can also be used as a tracing agent for easy urine

detection of drug abusers.

[0020]

The amount of the dye indicator used in the dosage form of the pharmaceutical formulation will vary with the particular dye used but, typically, the dye indicator is used in an amount of 0.01 to 20% by weight and, preferably, 0.1 to 10% by weight, and, most preferably, 0.1 to 5% by weight, based on the weight of a dosage form of the pharmaceutical formulation.

[0021]

The granules, beads, mini-tablets and tablets of the malodorous agent and/or dye indicator and of the drug formulations containing the malodorous agent and/or dye indicator can be made by various known pharmaceutical processes, such as roller compacting, and solution/slurry/powder layering in a fluid bed or other appropriate coating equipment, and compressing in a tablet press. In a particularly preferred embodiment, core seeds such as non-pareil seeds are coated with a layer of the malodorous agent and/or dye indicator and a barrier coating is applied to the layered core seeds.

[0022]

The barrier coating applied to the granules, beads or mini-tablets containing the malodorous agent and/or dye indicator or to granules, beads, mini-tablets or tablets of drug formulations containing the malodorous agent and/or dye indicator to minimize or prevent leakage of the agent and dye and to minimize absorption of the agent and dye under normal conditions of dosage administration can be a protective coating, enteric coating or sustained release coating or various combinations of these coatings. In a preferred embodiment, granules, beads or mini-tablets containing the malodorous agent and/or dye indicator and not containing the drug are coated with a non-dissolving pharmaceutically acceptable polymer coating which

does not dissolve or release under conditions existing in the GI tract. With such a coating, the malodorous agent and/or dye indicator is not released in the human body when properly administered and is released only when a drug formulation including the granules, beads or mini-tablets coated with the non-dissolving coating is crushed for non-prescribed purposes.

[0023]

The barrier coating may be applied by conventional coating techniques such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions.

[0024]

Materials useful as a protective coating are well-known in the art and include, for example, cellulose derivatives such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, and pH dependent cationic polymers soluble in gastric fluid up to pH 5.0 such as those sold under the trademarks EUDRAGIT E 100 and EUDRAGIT EPO. The suggested coating levels are from 1 to 6%, preferably 2-4% (w/w).

[0025]

The enteric coating layer can be any pH-sensitive polymer, which dissolves at a pH greater than 4.5, after a certain delayed time, or after the coated unit passes through the stomach. The preferred delay time is in the range of two to six hours. Suitable enteric polymers include cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, and co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, materials sold under the trademarks EUDRAGIT L100, EUDRAGIT

L100-55, EUDRAGIT L 30 D-55 or EUDRAGIT S100 or similar compounds used to obtain enteric coatings. The suggested coating levels are from 1 to 6%, preferably 2-4% (w/w).

[0026]

The enteric polymers can be modified by mixing with other known coating products that are not pH sensitive to provide sustained controlled release. Examples of such coating products include the neutral methacrylic acid esters with a small portion of trimethylammonioethyl methacrylate chloride, sold currently under the trademarks EUDRAGIT RL 30 D, EUDRAGIT RL PO, EUDRAGIT RL 100, EUDRAGIT RS 30 D and other pH independent coating products.

[0027]

The pharmaceutically acceptable coating that does not dissolve in the GI tract includes cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, poly(ethyl acrylate), poly (methyl methacrylate), and poly(trimethylammonioethylmethacrylate chloride). Suitable coating levels are those that prevent premature leakage of the malodorous/coloring (dye) agent and depend on the coating used. Coating levels range, for example, from 1 to 60% (w/w).

[0028]

An overcoating layer can further optionally be applied to the composition of the present invention. OPADRY®, OPADRY II® (sold by Colorcon) and corresponding color and colorless grades from Colorcon can be used to protect the pellets from being tacky and to provide color to the product. Additionally, Kollicoat IR (sold by BASF) with or without colorants and opacifiers can be used as an overcoating layer. The suggested levels of protective or color coating are from 1 to 6%, preferably 2-3% (w/w).

[0029]

In an alternative embodiment, insoluble particulate matter is used in the pharmaceutical formulations to hinder drug abusers from extracting the drug from the dosage units, to deter drug abusers, because of the insoluble particulate matters, from injecting the formulations intravenously, and to hinder the injection because of needle blocking. Suitable fine solid particulate materials include, but are not limited to, Noveon® AA-1 polycarbophil, Ethocel® FP, methacrylic acid copolymer (e.g., Eudragit® L100-55, Eudragit® S100), microcrystalline cellulose (e.g., Avicel® PH 102), sodium starch glycolate, crospovidone, croscarmellose sodium, talcum, and silicon dioxide. The size of the particles is selected such that the particles are easily suspended in the extraction media to hinder the extraction and block a needle while injecting. The usual particle size is from 1 μm to 150 μm and, preferably, from 1 μm to 50 μm.

[0030]

The insoluble, fine particles can be included in the coated granules, beads or mini-tablets of the malodorous agent and/or dye indicator or with granules, beads, mini-tablets or tablets containing the drug of interest in combination with the malodorous agent and/or dye indicator as described above. Alternatively, the insoluble, fine particles can be encapsulated or compressed with the coated granules, beads or mini-tablets or drug of interest.

[0031]

The water-insoluble agent is used in an amount of from 5 to 80% by weight and, preferably, from 5 to 40% by weight, and, most preferable, from 5 to 10% by weight, based on the weight of a dosage form of the pharmaceutical formulation into which the agent is incorporated.

[0032]

[EXAMPLES]

The following examples are presented to illustrate embodiments of the invention. The invention, however, is not limited to these embodiments but, instead, includes all those embodiments within the spirit and scope of the intended claims.

[0033]

Example 1

The following formulation is used to layer the agent with a disagreeable odor (skatole) onto sugar spheres. Nonpareil seeds (30/35 mesh, Paulaur Corp., NJ), 6.8 kg are put into a FLM-15 fluid bed processor with a 9" Wurster column and fluidized at 60°C. The coating system containing skatole and HPMC E5 Premium (Dow Chemical) as a binder is sprayed onto the seed under suitable conditions. Almost no agglomeration and no fines are observed with a yield of at least 98%. Subsequently, a barrier coat is applied onto the skatole-loaded beads to ensure no leakage of skatole and to prevent the absorption of the agent in the gastrointestinal tract.

TABLE 1

Ingredients	Amount (%)
Non-pareil seeds	89.4
Skatole	10.0
Methocel® E5 Premium	0.6
Water	*

* removed during processing

[0034]

Example 2

The following formulation is used to coat the beads from Example 1 with Eudragit E100 and subsequently with Eudragit FS30D. 2 kg of beads (contain skatole) are loaded into a fluid

bed processor with a Wurster column equipped with a precision coater (MP 2/3, Niro Inc.). The Eudragit E100 spray suspension is prepared by dispersing Talc and dissolving the Eudragit E100 in the organic solvent system (acetone: isopropyl alcohol 50:50). Under suitable fluidization conditions, the coating system is sprayed onto the fluidized pellets. Subsequently, the coating dispersion is prepared by dispersing Triethyl citrate, Talc and EUDRAGIT FS30D into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion is sprayed onto the fluidized Eudragit E100 coated pellets. The spraying is continued until the targeted coating level is achieved (20 microns). The coated pellets are dried at 30-35°C for 5 minutes before stopping the process. Talc is added to the Eudragit FS30D coated beads to prevent the agglomeration of the beads. The enteric-coated pellets are tested in acidic medium and no leakage of skatole is observed. The beads from this example can be encapsulated with sustained-release beads or immediate-release beads. Also, the beads from the Example 2 may be compressed with sustained-release or immediate-release matrix tablet formulation to reduce the abuse potential.

TABLE 2

Ingredient	Amount (%)
Beads containing skatole	62.0
Eudragit® E100	5.0
Talc	1.0
Acetone	*
Isopropyl alcohol	*
Eudragit® FS30D	26.24
Triethyl citrate	0.76
Talc	3.0
Water	*
Talc**	2.0

* removed during processing

** Talc is used to dry blend with beads to minimize the static charge and to prevent the agglomeration during the storage.

[0035]

Example 3

The following formulation is used to layer the drug onto sugar spheres. Nonpareil seeds (30/35 mesh, Paulaur Corp., NJ), 6.8 kg are put into a FLM-15 fluid bed processor with a 9" Wurster column and fluidized at 60°C. The suspension of mixed amphetamine salts (MAS) with 1% HPMC E5 Premium (Dow Chemical), and skatole is sprayed onto the seed under suitable conditions. Almost no agglomeration and no fines are observed with a yield of at least 98%. The drug-loaded cores are used for the enteric coatings and sustained release coatings.

TABLE 3

Ingredients	Amount (%)
Nonpareil seed	82.00
mixed amphetamine salts	11.40
METHOCEL® E5 Premium	0.60
Skatole	3.0
Water	*

* removed during processing

[0036]

Example 4

The following formulation is used to coat the mixed amphetamine salts loaded pellets from Example 3 with the EUDRAGIT.RTM. L 30D-55 (Rohm Pharma, Germany) coating dispersion. 2 kg of MASL pellets are loaded into a fluid bed processor with a reduced Wurster column equipped with a precision coater (MP 2/3, Niro Inc.). The coating dispersion is

prepared by dispersing triethyl citrate, talc and EUDRAGIT L 30D-55 into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion is sprayed onto the fluidized MASL pellets. The spraying is continued until the targeted coating level is achieved (20 microns). The coated pellets are dried at 30-35°C for 5 minutes before stopping the process. The pellets are further blended with Talc to prevent the agglomeration during the storage. The enteric coated amphetamine pellets are tested at different pH buffers by a USP paddle method. The drug content is analyzed using HPLC. The results show that the enteric coating delays the drug release from the coated pellets until after exposure to pH 6 or higher.

TABLE 4

Ingredients	Amount (%)
Amphetamine beads from Example 3	68.10
EUDRAGIT® L 30D-55	24.78
Triethyl citrate	2.52
Talc**	2.60
OPADRY® beige	2.0
Water	*

* removed during processing

** Talc is blended with the pellets to prevent the agglomeration during storage.

[0037]

Example 5

The following formulation is used to coat the amphetamine pellets from Example 3 with the EUDRAGIT.FS30D (Rohm Pharma, Germany) coating dispersion. The amphetamine pellets (2 kg) are loaded in a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion is prepared by

dispersing triethyl citrate, talc and EUDRAGIT.FS30D into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion is sprayed onto the fluidized amphetamine pellets. The spraying is continued until the targeted coating level is achieved. The coated pellets are dried at 30-35°C for 5 minutes before stopping the process. The enteric-coated amphetamine pellets are tested using a USP paddle method at different pH buffers. The drug content is analyzed using HPLC. The enteric coating delays the drug release for several hours from the coated pellets until the pH value reached 6.8 or higher.

TABLE 5

Ingredients	Amount (%)
Amphetamine pellets from Example 3	70.00
EUDRAGIT® FS30D	26.04
Triethyl citrate	0.76
Talc	3.00
Water	*

*removed during processing

[0038]

Example 6

The following formulation is selected to coat the enteric coated amphetamine pellets. Coated amphetamine pellets from Example 4 or coated amphetamine pellets from Example 5 (2 kg of either) are loaded into a fluid bed processor with a reduced Wurster column (GPGC- 1 5, Glatt). The coating dispersion is prepared by mixing SURELEASE (Colorcon) and water for at least 15 minutes prior to spraying. Under suitable fluidization conditions, the coating dispersion is sprayed onto the fluidized pellets. The spraying is continued until the targeted coating level is achieved. The coated pellets are coated with a thin

layer of OPADRY white (Colorcon) (2%) to prevent the tackiness of the coated pellets during storage. The coated pellets are then dried at 35-40°C for 10 minutes before discharging from the bed. The drug dissolution from both coated pellets is performed using a USP paddle method at different pH buffers. The drug content is analyzed using HPLC. The 12% SURELEASE. coating sustains the drug release from both EUDRAGIT L 30D-55 and Eudragit FS30D coated pellets at pH 7.5 buffer, while the Eudragit coating delays the drug release up to 2 hours after the buffer is switched from pH 1 to pH 7.5.

TABLE 6

Ingredients	Amount(%)
Enteric coated amphetamine beads from Example 4 or 5	86.00
SURELEASE®	12.00
Water	*
OPADRY white	2.00

* removed during processing

[0039]

Example 7

The following formulation is used to layer the drug onto sugar spheres. Nonpareil seeds (30/35 mesh, Paulaur Corp., NJ), 6.8 kg are put into a FLM-15 fluid bed processor with a 9" Wurster column and fluidized at 60°C. The suspension of drug with abuse potential with 1% HPMC E5 Premium (Dow Chemical) as a binder is sprayed onto the seed under suitable conditions. Almost no agglomeration and no fines are observed with a yield of at least 98%. The drug-loaded cores are optionally used to prepare enteric coatings and/or sustained release coatings similar to Examples 4, 5 and 6. The immediate-release beads obtained from Example 7, the delayed-release beads (beads from Example 7 further coated with enteric material), the sustained-

release beads (beads from Example 7 further coated with sustained-release material), and any combination of beads can be encapsulated with beads from Example 2 to reduce the abuse potential.

TABLE 7

Ingredients	Amount (%)
Nonpareil seed	87.90
Morphine sulfate	11.40
METHOCEL® E5 Premium	0.6
Water	*

*removed during processing

[0040]

Example 8 (Tablet formulation of a high potency compound)

The following is a sustained-release formulation containing both morphine sulfate and oxycodone. All the ingredients are blended in a V-shaped blender for 10 minutes and subsequently blended for additional 10 minutes with the intensifier bar on. The powder blend is lubricated with magnesium stearate for 3 minutes. The lubricated powder blend is compressed into tablets.

TABLE 8

Ingredients	Amount (%)
Polyox	30.00
Microcrystalline cellulose	18.2
Morphine sulfate	20.0
Oxycodone hydrochloride	11.3
Skatole	5.00
Fumaric acid	5.00
Glyceryl behenate	10.00
Magnesium stearate	0.50

[0041]

Example 9

The following formulation is used to coat the core tablet from Example 8 for odor masking purpose. The coating solution is prepared by dissolving the Eudragit E100 in a solvent system (acetone:isopropyl alcohol 50:50). The coating process is carried out in a side-vented coating pan.

TABLE 9

Ingredients	Amount (%)
Core Tablet from Example 8	85.5
EUDRAGIT® E100	15.0
Acetone	*
Isopropyl alcohol	*

* removed during the process

[0042]

Example 10

Similar procedure to Example 8 is used for this sustained-release formulation example. Blend first five ingredients in a V-Blender for 10 minutes and subsequently blend for additional 10 minutes with the intensifier bar on. Add magnesium stearate to mix and blend for additional 2 minutes. Press tablets on a convention or other rotary tablet press to give 75 to 500 mg tablets, depending on desired dose (e.g., 15 mg, 30 mg, 60 mg, and 100 mg strength). The core tablets produced are coated with Eudragit E100 (see Example 9) for odor masking purposes.

TABLE 10

Ingredients	Amount (%)
Polyox	30.0
Microcrystalline Cellulose	29.0
Dicalcium phosphate (FujiCalin)	15.0
Morphine sulfate	20.0
Isovaleric acid	5.0
Magnesium stearate	1.0

[0043]

Example 11

The following formulation is used to layer the malodorous agent (isovaleric acid) and the indicator dye (tartrazine) onto sugar spheres. Nonpareil seeds (30/35 mesh, Paulaur Corp., NJ), 6.8 kg are put into a Glatt GPCG-15 fluid bed processor with a 9" Wurster column and fluidized at 60°C. The coating system containing denatonium saccharide, tartrazine, and HPMC E5 Premium (Dow Chemical) as a binder is sprayed onto the seed under suitable conditions. Almost no agglomeration and no fines are observed with a yield of at least 98%.

TABLE 11

Ingredients	Amount (%)
Nonpareil seed	89.4
Isovaleric acid	5.0
Tartrazine	5.0
Hydroxypropyl methyl cellulose	0.6
Water	*

* removed during processing

[0044]

Example 12

The following formulation is used to coat the beads from Example 11 with cellulose acetate as a barrier coat to ensure against leakage of the malodorous agent and tartrazine dye and to minimize the absorption of these agents in the gastrointestinal tract. 3.6 kg of the beads are loaded into a fluid bed processor with a Wurster column equipped with an HS nozzle (GPCG-15, Glatt Air Techniques). Cellulose acetate and triethyl citrate are dissolved in an organic solvent system (acetone: isopropyl alcohol 80:20). Under suitable fluidization conditions, the coating system is sprayed onto the fluidized pellets. The beads from this example can be encapsulated with sustained-release beads, immediate-release beads, delayed-release beads, or the combination of any of these types of beads. Also, the beads can be compressed with a sustained-release or immediate-release matrix tablet formulation to reduce the abuse potential.

TABLE 12

Ingredients	Amount (%)
Beads from Example 11	70.0
Cellulose acetate	27.0
Triethyl citrate	3.0
Acetone:isopropyl alcohol (80:20)	*

* removed during processing

[0045]

Insoluble fine particles can be added to the formulations of Examples 1, 3, 7 and 8 to obtain beads containing a malodorous agent, dye indicator and insoluble fine particles or drug loaded beads containing active pharmaceutical ingredient (API) and insoluble fine particles. Alternatively, the

insoluble fine particles can be encapsulated or compressed with coated granules, beads or mini-tablets or drugs of interest.

[0046]

Example 13

This example describes the preparation of a transdermal patch dosage form of the invention. A methylphenidate-polymer mixture is prepared by combining 20 parts of methylphenidate, 1 part of skatole, 1 part of tartrazine, 1.3 part of lecithin, 1 part of dipropylene glycol, 0.8 part of oleic acid, 2.5 parts of polydimethylsiloxane, 63.6 parts of polyacrylate, and > 85.6 parts of polysiloxane, and mixed well in an appropriate container. Methylphenidate is added as a solution in ethyl acetate mixed together with the polyacrylate. The resulting composition has the ingredient concentrations on a dry basis, after removal of volatile process solvents, which is shown in Table 13. The formulation is then transferred to a coating operation where it is coated onto a protective release liner at a controlled specified thickness. The coated product is then passed through an oven in order to drive off all volatile processing solvents. The dried product on the release liner is then joined to the backing material and wound into rolls. Appropriate size and shape dosage units are die-cut from the roll material and then pouched.

TABLE 13

Ingredients	Amount (%)
polysiloxane (Dow CorningSilicone Adhesive X7-4919)	42.8
polyacrylate (National Starch Acrylic Adhesive, Duro-Tak 80-1194)	28.6
polydimethylsiloxane fluid (Dow Corning 360 medical fluid)	2.5

lecithin	1.3
propylene glycol	1.0
dipropylene glycol	1.0
oleic acid	0.8
methylphenidate base	20.0
Skatole	1.0
tartrazine	1.0

ADVANTAGES OF THE INVENTION

[0047] The present invention provides a combination of three effective approaches to reduce the abuse potential for dosage forms of psychoactive drugs. Malodorous agents, dye indicators and/or fine particulate matter are added to dosage forms of prescription psychoactive drug formulations to reduce the abuse potential of the drug formulations. The malodorous agents and dye indicators may be incorporated into deterrent beads having a barrier coating. The beads can be fabricated separately from the manufacturing of the pharmaceutical dosage form of reduced abuse potential. Such "universal" deterrent beads can shorten product development time and minimize the impact of the malodorous agents/dye indicators on product performance. The deterrent beads can also be formulated so that the malodorous agents/dye indicators are not released under normal administration conditions to minimize possible adverse effects from these agents.

WHAT IS CLAIMED IS:

1. A dosage form having reduced abuse potential comprising a psychoactive drug as an active pharmaceutical ingredient, and one or more of:

(1) a malodorous agent in a form which does not create a disagreeable odor when the dosage form of the drug is properly administered, but which creates a disagreeable odor when crushed or extracted and nasally, by inhalation, orally, buccally or sublingually administered;

(2) an indicator dye in a form which does not create color when the dosage form of the drug is properly administered, but which colors or stains human tissue when crushed or extracted; and

(3) fine insoluble particulate matter.

2. The dosage form according to claim 1, wherein said one or more malodorous agent, indicator dye and fine insoluble particulate matter is contained in a granule, bead or tablet.

3. The dosage form according to claim 2, wherein said granule, bead or tablet is coated with a pharmaceutically acceptable protective coating, enteric coating or sustained release coating.

4. The dosage form according to claim 3, wherein said protective coating is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, and pH dependent cationic polymers soluble in gastric fluid up to pH 5.0.

5. The dosage form according to claim 3, wherein said enteric coating is a pH-sensitive polymer which dissolves at a pH greater than 4.5, after a selected delayed time, or after the coated unit passes through the stomach.

6. The dosage form according to claim 3, wherein said pH sensitive polymer is selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, and co-polymerized methacrylic acid/methacrylic acid methyl esters.

7. The dosage form according to claim 2, wherein said granule, bead or tablet is coated with a coating that does not dissolve in the gastrointestinal tract.

8. The dosage form according to claim 7, wherein the coating that does not dissolve in the gastrointestinal tract is selected from the group consisting of cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, poly(ethyl acrylate), poly (methyl methacrylate), and poly(trimethylammonioethylmethacrylate chloride).

9. The dosage form according to claim 1, wherein said malodorous agent is selected from the group consisting of valerian herb crude extract, isovaleric acid, betaine, anisole, garlic oil, garlic crude extract, fish oil, skatole, methylarginine, taurine, trimethylamine, triethylamine, and 3-methyl 2-hexanoic acid.

10. The dosage form according to claim 9, wherein said malodorous agent is selected from the group consisting of isovaleric acid and skatole.

11. The dosage form according to claim 1, wherein said indicator dye is selected from the group consisting of allura red, amaranth, brilliant blue, canthaxanthin, carmine, carmoisine, carotene, curcumin, erythrosine, green S, indigo carmine, iron oxide black, iron oxide red, iron oxide yellow,

patent blue, phloxine O, ponceau 4R, quinoline yellow, riboflavin, sunset yellow, tartrazine, titanium dioxide, vegetable carbon black, annatto, beet, black carrot, black currant, caramel, carmine, carmine lake, chlorophyll, cochineal, elderberry, grapeskin/grape juice, malt, paprika, red cabbage, turmeric, and anthocyanins.

12. The dosage form according to claim 11, wherein said indicator dye is tartrazine.

13. The dosage form according to claim 1, wherein said fine insoluble particulate matter is selected from the group consisting of polycarbophil, methacrylic acid copolymer, microcrystalline cellulose, sodium starch glycolate, crospovidone, croscarmellose sodium, talcum, and silicon dioxide.

14. The dosage form according to claim 1 which is a capsule.

15. The dosage form according to claim 14, wherein said one or more malodorous agent, indicator dye and fine insoluble particulate matter is contained in a granule, bead or tablet.

16. The dosage form according to claim 15, wherein said granule, bead or tablet is coated with a pharmaceutically acceptable protective coating, enteric coating or sustained release coating.

17. The dosage form according to claim 16, wherein said protective coating is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, and pH dependent cationic polymers soluble in gastric fluid up to pH 5.0.

18. The dosage form according to claim 16, wherein said enteric coating is a pH-sensitive polymer which dissolves at a pH greater than 4.5, after a selected delayed time, or after the coated unit passes through the stomach.

19. The dosage form according to claim 16, wherein said pH sensitive polymer is selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, and co-polymerized methacrylic acid/methacrylic acid methyl esters.

20. The dosage form according to claim 15, wherein said granule, bead or mini-tablet is coated with a coating that does not dissolve in the gastrointestinal tract.

21. The dosage form according to claim 20, wherein the coating that does not dissolve in the gastrointestinal tract is selected from the group consisting of cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, poly(ethyl acrylate), poly (methyl methacrylate), and poly(trimethylammonioethylmethacrylate chloride).

22. The dosage form according to claim 14, wherein said malodorous agent is selected from the group consisting of valerian herb crude extract, isovaleric acid, betaine, anisole, garlic oil, garlic crude extract, fish oil, skatole, methylarginine, taurine, trimethylamine, triethylamine, and 3-methyl 2-hexanoic acid.

23. The dosage form according to claim 22, wherein said malodorous agent is selected from the group consisting of isovaleric acid and skatole.

24. The dosage form according to claim 14, wherein said indicator dye is selected from the group consisting of allura red, amaranth, brilliant blue, canthaxanthin, carmine, carmoisine, carotene, curcumin, erythrosine, green S, indigo carmine, iron oxide black, iron oxide red, iron oxide yellow, patent blue, phloxine O, ponceau 4R, quinoline yellow, riboflavin, sunset yellow, tartrazine, titanium dioxide, vegetable carbon black, annatto, beet, black carrot, black currant, caramel, carmine, carmine lake, chlorophyll, cochineal, elderberry, grapeskin/grape juice, malt, paprika, red cabbage, turmeric, and anthocyanins.

25. The dosage form according to claim 24, wherein said indicator dye is tartrazine.

26. The dosage form according to claim 14, wherein said fine insoluble particulate matter is selected from the group consisting of polycarbophil, methacrylic acid copolymer, microcrystalline cellulose, sodium starch glycolate, crospovidone, croscarmellose sodium, talcum, and silicon dioxide.

27. The dosage form according to claim 1 which is a tablet.

28. The dosage form according to claim 27, wherein said one or more malodorous agent, indicator dye and fine insoluble particulate matter is contained in a granule or bead.

29. The dosage form according to claim 28, wherein said granule or bead is coated with a pharmaceutically acceptable protective coating, enteric coating or sustained release coating.

30. The dosage form according to claim 29, wherein said protective coating is selected from the group consisting of

hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, ethyl cellulose aqueous dispersions and pH dependent cationic polymers soluble in gastric fluid up to pH 5.0.

31. The dosage form according to claim 29, wherein said enteric coating is a pH-sensitive polymer which dissolves at a pH greater than 4.5, after a selected delayed time, or after the coated unit passes through the stomach.

32. The dosage form according to claim 29, wherein said pH sensitive polymer is selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, and co-polymerized methacrylic acid/methacrylic acid methyl esters.

33. The dosage form according to claim 28, wherein said granule, bead or mini-tablet is coated with a coating that does not dissolve in the gastrointestinal tract.

34. The dosage form according to claim 33, wherein the coating that does not dissolve in the gastrointestinal tract is selected from the group consisting of cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, poly(ethyl acrylate), poly (methyl methacrylate), and poly(trimethylammonioethylmethacrylate chloride).

35. The dosage form according to claim 27, wherein said malodorous agent is selected from the group consisting of valerian herb crude extract, isovaleric acid, betaine, anisole, garlic oil, garlic crude extract, fish oil, skatole, methylarginine, taurine, trimethylamine, triethylamine, and 3-methyl 2-hexanoic acid.

36. The dosage form according to claim 35, wherein said malodorous agent is selected from the group consisting of isovaleric acid and skatole.

37. The dosage form according to claim 27, wherein said indicator dye is selected from the group consisting of allura red, amaranth, brilliant blue, canthaxanthin, carmine, carmoisine, carotene, curcumin, erythrosine, green S, indigo carmine, iron oxide black, iron oxide red, iron oxide yellow, patent blue, phloxine O, ponceau 4R, quinoline yellow, riboflavin, sunset yellow, tartrazine, titanium dioxide, vegetable carbon black, annatto, beet, black carrot, black currant, caramel, carmine, carmine lake, chlorophyll, cochineal, elderberry, grapeskin/grape juice, malt, paprika, red cabbage, turmeric, and anthocyanins.

38. The dosage form according to claim 37, wherein said indicator dye is tartrazine.

39. The dosage form according to claim 27, wherein said fine insoluble particulate matter is selected from the group consisting of polycarbophil, methacrylic acid copolymer, microcrystalline cellulose, sodium starch glycolate, crospovidone, croscarmellose sodium, talcum, and silicon dioxide.

40. The dosage form according to claim 1 which is a transdermal patch.

41. The dosage form according to claim 1 which is a liquid suspension.

42. A deterrent particle to be incorporated into a capsule or tablet containing a drug of abuse and comprising a malodorous

agent contained in a granule, bead or tablet coated with a pharmaceutically acceptable substance which when digested dissolves, if at all, after reaching the small intestine.

43. A deterrent particle to be incorporated into a capsule or tablet containing a drug of abuse and comprising a dye contained in a granule, bead or tablet coated with a pharmaceutically acceptable substance which when ingested dissolves, if at all, after reaching the small intestine.